REMARKS

This amendment is in response to the Office Action, dated April 17, 2006, ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Claims 1-9, 11-20, 22-28 and 57-62 are pending. Claims 1-9, 12-20, 57-58 and 60-61 were objected to and claims 1-9, 11-20, 22-28 and 57-62 were rejected. Claims 1, 12, 23, 26, 29 and 32 have been amended; claims 10, 21, and 29-34 were previously withdrawn; and claims 35-56 were previously canceled. Following entry of the present amendment, amended claims 1-9, 11-20, 22-28 and 57-62 are pending. No new matter has been added. Allowance and reconsideration of the application in view of Applicant's amendment and the ensuing remarks are respectfully requested. Applicant reserves the right to pursue other aspects of the present invention in later filed applications.

The specification has been amended to correct an obvious typographical error in the chemical structure of arzoxifene; changing an "-OH" to "-OCH_3."

Claims 1, 12, 23, 26, 29 and 32 have been amended to recite that the method is a method of "inhibiting tumor growth" of androgen-independent prostate cancer. Support for this amendment may be found throughout the specification; for example, pages 11-12.

Claims 29 and 32 have also been amended to correct the chemical structure of arzoxifene by changing an "-OH" to "-OCH_3."

Examiner objected to claims 1-9, 12-20, 57-58 and 60-61 as containing non-elected subject matter. Applicant respectfully submits that Claims 11, 22-28, 59 and 62 are allowable; therefore, generic claims 1-9, 12-20, 57-58 and 60-61, encompassing additional species are allowable. Thus, Applicant respectfully requests Examiner to withdraw this objection.

Examiner rejected claims 1-9, 11-20, 22-28 and 57-62 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,632,447 (Steiner *et al.*). Examiner first states that unless the reference teaches to the contrary, the term "prostate cancer" is "taken to mean both androgen-dependent and independent prostate cancer" because "prostate cancer" as used in the art includes any and all types of prostate cancer. Examiner also states that the term "treatment" as used by Steiner *et al.* refers to "a method that suppresses or inhibits tumor metastasis and/or primary tumor size," because that is the traditional meaning. Examiner found that Steiner *et al.* teach the administration of antiestrogens as a method of treating a subject with prostate cancer. Additionally, Examiner found that Steiner *et al.* teach the use of raloxifene as a "chemopreventive/treatment agent." Furthermore, Steiner *et al.* was found to teach methods of administration, dosing ranges and the use of the compound's analogs. With respect to claims 1-9, 11-20, 22-28, and 57-62 this rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP §2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Furthermore, a patent cannot be relied upon as anticipatory to the extent that the scope of its disclosure does not reasonably suggest those aspects relied upon in the rejection. *See Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); MPEP §2123.

Applicant respectfully submits that the term "prostate cancer" as used by Steiner *et al.* does not refer to androgen-independent prostate cancer (AIPC). Steiner *et al.*, taken as a whole, speaks to chemoprevention of prostate cancer and does not broadly encompass the treatment of AIPC. First, Steiner *et al.* do not mention AIPC as a form of prostate cancer that can be treated by their methods. Second, Steiner *et al.* refer to suppressing or inhibiting latent prostate cancer or treating subjects having an elevated risk of developing prostate cancer. (See Steiner *et al.* col. 1, lines 24-25 and col. 3, lines 22-29.) Moreover, the background of the invention by Steiner *et al.* discusses preventing prostate cancer, developing chemoprevention strategies, delaying or preventing the onset of prostate carcinoma, and treating benign prostatic hyperplasia.

The background does not discuss treating active prostate cancer, androgen-dependent prostate cancer or androgen-independent prostate cancer.

Applicant also respectfully submits that "treat" or "treatment" as used in Steiner *et al.* do not include "a method that suppresses or inhibits tumor metastasis and/or primary tumor size," because taken as a whole, the use of the terms "treat" or "treatment" by Steiner *et al.* refers to chemoprevention, suppression of latent cancers, or treatment of subjects with elevated risk of developing cancer. Steiner *et al.* described the use of raloxifene as a "prostate chemopreventive agent and prostate intraepithelial neoplasia agent." (See Steiner *et al.*, col. 4, lines 9-12.) It can be plainly concluded that raloxifene is used to prevent prostate cancer as it was described as a chemopreventive agent. Moreover, raloxifene's use as a prostate intraepithelial neoplasia agent also implies its use to prevent prostate cancer since prostate intraepithelial neoplasia is viewed as a risk factor for developing prostate cancer. (See Steiner *et al.* col. 9, lines 13-19.) Furthermore, examples 1, 3, 5, 7 in Steiner *et al.* describe chemoprevention and do not describe suppression or inhibition of tumor metastasis and/or primary tumor size. Example 6 in Steiner *et al.* only shows suppression of hormone sensitive tumor growth in athymic nude mice. Example 8 in Steiner *et al.* describes regression of high grade prostate intraepithelial neoplasia (HGPIN) and prostate cancer chemoprevention. Thus, the treatment contemplated by Steiner *et al.* is treatment of intraepithelial neoplasia or subjects with high risk of developing prostate cancer. Accordingly, the use of "treat" and "treatment" by Steiner *et al.* does not broadly encompass the treatment of AIPC and more specifically, the inhibition or suppression of AIPC tumor growth.

In sum, Steiner *et al.* do not teach each element of Applicant's claims, as amended. Furthermore, because Applicant's claimed methods are patentable, the dependent claims are similarly patentable. In light of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §102(e).

Examiner rejected claims 1-9, 11-20 and 22-28 under 35 U.S.C. §103(a) as being obvious over Lau *et al.* (Cancer Research, 60:3175-3185, 2000) in view of Neubauer *et al.* (The Prostate, 27:220-229, 1995). Lau *et al.* was cited to show that AIPC cell lines DU145 and PC3 express ERβ and the potential of antiestrogens as

prostate cancer therapies were suggested because the growth-inhibitory action of antiestrogens on those cell lines was observed. Neubauer *et al.* was cited to show that raloxifene inhibited metastasis from the primary tumor and "further studies are needed to define the maximal antitumor efficacy," (emphasis by examiner). Examiner quoted, "[i]nasmuch as the metastatic processes in the rat PAIII model may be similar to human urogenital malignancies, raloxifene deserves consideration for clinical evaluation in humans," (emphasis by Examiner). As such, Examiner concluded that it would have been obvious to "further evaluate raloxifene in models of AIPC with a possible mechanism being inhibition of ERβ," and "to use higher doses and different treatment regimes." Examiner also noted that Neubauer used a maximum dosage of 2.2 mg/day on the rats and the present invention claims doses that are 5-130 times higher. Examiner asserted that since 2.2 mg/day can inhibit metastasis, it would have been obvious to increase the dose to treat AIPC.

Examiner was not persuaded by Applicant's previous arguments against obviousness. First, Examiner found that even though the dosage used in Neubauer *et al.* did not inhibit tumor growth, it did not teach away from further studies using higher doses or treatment schedules. In addition to the above, Examiner also quoted the abstract stating that Neubauer *et al.* "support the contention that raloxifene represents a class of active antimetastatic agents with potential efficacy in the treatment of hormone-insensitive human prostatic cancer." (Emphasis by Examiner.) Examiner stated that Neubauer *et al.* did not mischaracterize the pathophysiology of the disease and the effect of the drug because Neubauer *et al.* "taught possible mechanism of the drug's affect on metastasis, not tumor suppression."

Examiner asserted that there is reasonable expectation of success based on Neubauer *et al.* because they taught the use of raloxifene to inhibit metastasis in one model system at an upper dose of 20 mg/kg and that further studies are needed to "define the maximal antitumor efficacy and mechanism of action of raloxifene in the treatment of [AIPC]." (Internal quotations omitted.) As such, Examiner stated that it would have been obvious to modify the model, dose and administration schedule in the treatment of AIPC.

In sum, Examiner stated that Neubauer *et al.* suggest all the limitations of the claims and provide motivation to practice them because one skilled in the art would know "a) Raloxifene is an antiestrogen; b) Estrogen receptors are present in prostate cancer tissue; c) Raloxifene is known to inhibit metastasis of androgen-independent prostate cancer at a dose of 20 mg/kg/day (2.2 mg/day); and d) Raloxifene at that dose does not stabilize the primary tumor." Thus, Examiner concluded that it would have been obvious to "increase the dosage and/or treatment schedule, use raloxifene in other prostate cancer models, and attempt to elucidate the mechanism of action, as suggested by the reference."

With respect to claims 1-9, 11-20 and 22-28, this rejection is respectfully traversed.

Three basic criteria must be met to establish a prima facie case of obviousness: (1) "there must be some suggestion or motivation...to combine reference teachings," (2) "there must be a reasonable expectation of success," and (3) *the prior art references "must teach or suggest all the claim limitations.*" MPEP §2142 (emphasis added). Furthermore, the suggestion or motivation to combine reference teachings must be found in the prior art and cannot be based solely on hindsight. MPEP §2145(X)(A). A reconstruction based on hindsight reasoning may be proper if takes account only knowledge which was within the level of ordinary skill in the art at the time of the claimed invention was made and does not include knowledge gleaned from applicant's disclosure. *See In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971).

Applicant respectfully submits that the combination of Lau *et al.* and Neubauer *et al.* does not render claims 1-9, 11-20 and 22-28 obvious under §103(a).

Applicant respectfully submits that Examiner erroneously characterized the dosage used by Neubauer *et al.* and as a result mistakenly believed that the dosage by Neubauer *et al.* was merely not large enough to exhibit antitumor effects. Applicant notes that the maximum dosage used by Neubauer *et al.* was 5.0 mg/day rather than 2.2 mg/day as stated by Examiner. The rats weighed between 110-125 grams (see page 222) and the largest dose was 40 mg/kg/day (see page 222 under "Effects of Raloxifene on Survival"). Accordingly, the largest dose was 5.0 mg/day. Second, a relevant inquiry is to the dosage relative to the body mass of the subject. Neubauer *et*

al. administered raloxifene at dosages of 2.0, 10.0, 20.0 and 40.0 mg/kg/day (see pages 222 and 223) to the rats. As shown in Example 2 in Applicant's specification, Applicant administered raloxifene at a dosage of 0.85 mg/kg/day to the mice, a dosage that is less than the lowest dosage administered by Neubauer *et al.* With this lower dosage, Applicant was able to show that raloxifene inhibited tumor growth in the rats (see Example 2 of the Specification, pages 11-12). Additionally, for exemplary purposes, the average weight for a human male in the United States is 191 pounds, which is approximately 87 kg (see Chartbook on Trends in the Health of Americans, page 42, by the U.S. Department of Health and Human Services; Exhibit A). Claims 2, 13, 24, and 27 of the present invention claim a dosage of about 10 mg to 300 mg per day. This dosage range given to an average male would be a dosage range of about 0.01mg/kg/day to about 3.45 mg/kg/day. Thus, contrary to Examiner's assertion that Applicant's claimed doses are 5-130 times higher than that disclosed by Neubauer *et al.*, Applicant's claimed doses are in fact less than three of the four doses (*i.e.*, 10, 20 or 40 mg/kg/day) used by Neubauer *et al.* Moreover, claims 3, 4, 5, 14, 15, and 16 claim dosages of 60 mg or 180 mg, which for an average male, is 0.69 or 2.07 mg/kg/day. These amounts are less than or approximately equal to the lowest dose described by Neubauer *et al.* While the doses by Neubauer *et al.* did not inhibit tumor growth, the smaller dose used by Applicant on his experimental mice (0.85 mg/kg/day) does in fact inhibit tumor growth. Therefore, even assuming *arguendo* that Neubauer *et al.* do not teach away from using higher doses to inhibit tumor growth, Neubauer *et al.* certainly do teach away from using the same or lower dose and Applicant's claimed dosing ranges. Applicant has used and has shown that a dose of 0.85 mg/kg/day has anti-tumor effects on androgen-independent xenograft model of human prostate tumor cells in mice.

Examiner quoted, "[i]nasmuch as the metastatic processes in the rat PAIII model may be similar to human urogenital malignancies, raloxifene deserves consideration for clinical evaluation in humans," but placed the emphasis on clinical evaluation in humans. However, the entire context of the statement must be considered. Neubauer *et al.* stated, "inasmuch as the metastatic processes...may be similar to human urogenital malignancies..." (emphasis added). A fair reading of this statement suggests that raloxifene deserves consideration for evaluating its effect on the

metastatic processes in humans. The statement by Neubauer *et al.* does not broadly encompass tumor inhibition or suppression, as suggested by Examiner. Indeed, Neubauer *et al.* provided data that raloxifene had "no activity against the *in vitro* colony formation activity of PAIII cells," and did not "inhibit tumor growth." Moreover, Neubauer *et al.* supported a contention that "raloxifene...has no direct cytoreductive activity." (See Neubauer *et al.*, page 227.)

Since Neubauer *et al.* did not teach the use of raloxifene for the inhibition or suppression of tumor growth of AIPC and taught away from using raloxifene to inhibit tumor growth of AIPC, one of skill in the art would not have been motivated to combine Neubauer *et al.* because there would not be any expectation of success. Even assuming that the combination was proper, Neubauer *et al.* and Lau *et al.* in combination do not teach or suggest each and every element of the claims. In light of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (213) 633-6869.

Respectfully submitted,

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By _____
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Enclosures:

Exhibit A: "Chartbook on Trends in the Health of Americans, by the U.S. Department of Health and Human Services, page 42."

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Health, United States, 2005

With Chartbook on Trends in the Health of Americans

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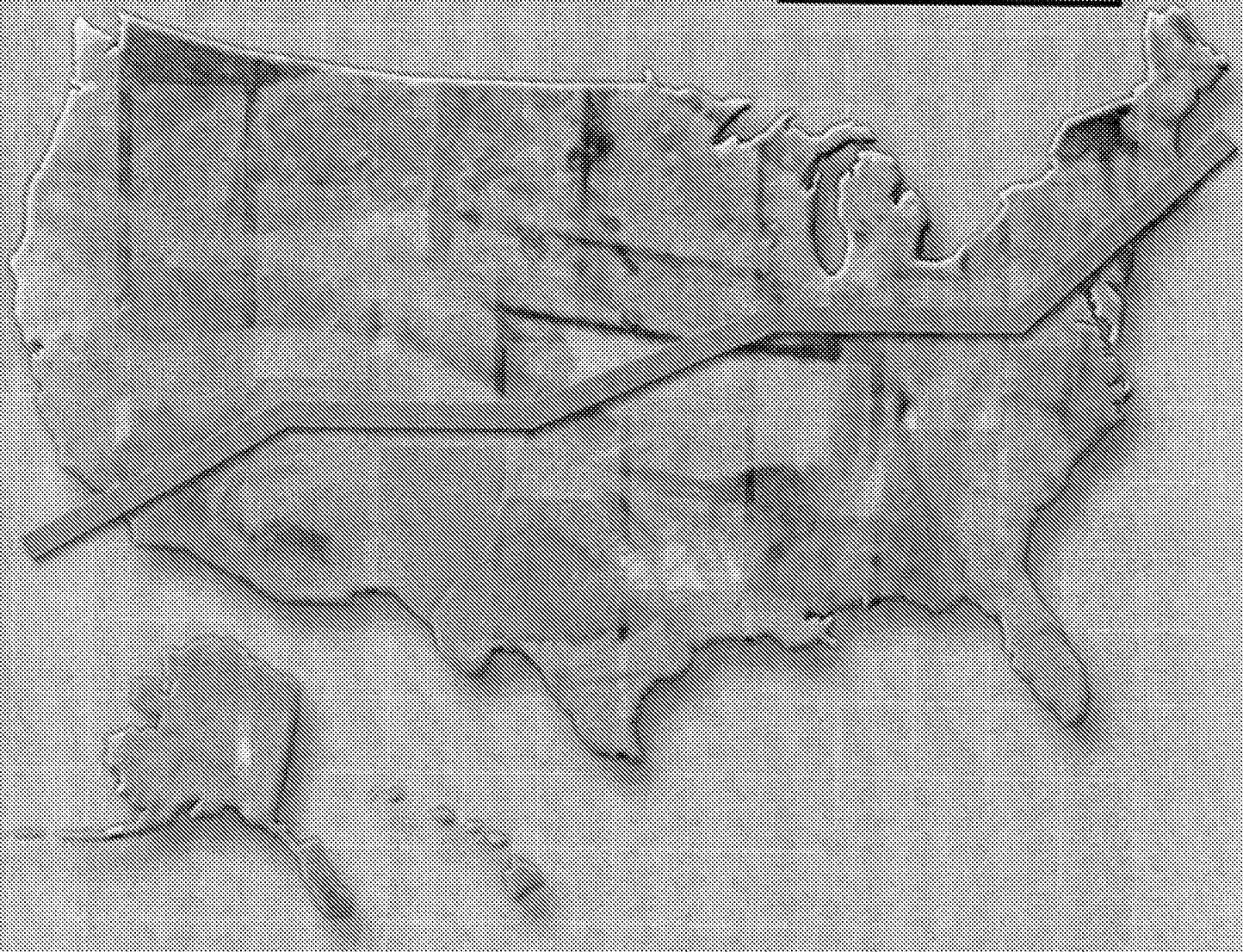

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

Overweight and Obesity

Epidemiologic and actuarial studies have shown that surplus body weight is associated with excess morbidity and mortality (1). Among adults, overweight and obesity elevate the risk of heart disease, diabetes, and some types of cancer. Overweight and obesity are also factors that increase the severity of disease associated with hypertension, arthritis, and other musculoskeletal problems (2). Obesity also has serious health consequences among younger persons. Among children and adolescents, obesity increases the risk of high cholesterol, hypertension, and diabetes (3). Diet, physical activity, genetic factors, environment, and health conditions all contribute to overweight in children and adults. The potential health benefits from reduction in the prevalence of overweight and obesity are of significant public health importance.

National Health and Nutrition Examination Surveys (NHANES) collect data from physical exams in a mobile examination center. Results from a series of NHANES indicate that the prevalence of overweight and obesity changed little between the early 1960s and 1976–80 (figure 15). Findings from the 1988–94 and 1999–2002 surveys, however, showed substantial increases in overweight and obesity among adults. The upward trend in overweight since 1980 reflects primarily an increase in the percent of adults 20–74 years of age who are obese. In 1999–2002, 65 percent of adults were overweight with 31 percent obese.

The percent of children (6–11 years of age) and adolescents (12–19 years of age) who are overweight has also risen. Among children and adolescents, the percent overweight has increased since 1976–80. In 1999–2002 about 16 percent of children and adolescents were overweight. The prevalence of overweight among adolescents varies by race and ethnicity. In 1999–2002, 14 percent of non-Hispanic white adolescents, 21 percent of non-Hispanic black adolescents, and 23 percent of Mexican-origin adolescents were overweight (4).

The prevalence of obesity varies among adults by sex, race, and ethnicity (*Health, United States, 2005,* table 73). In 1999–2002, 28 percent of men and 34 percent of women 20–74 years of age were obese. The prevalence of obesity among women differed significantly by racial and ethnic group. In 1999–2002 one-half of non-Hispanic black women were obese compared with nearly one-third of non-Hispanic white women. In contrast, the prevalence of obesity among men differed little by race and ethnicity (28–29 percent).

The rise in overweight and obesity is reflected in the average weight of adult men and women in the United States (5). Adult men and women are roughly an inch taller than they were in 1960–62, but are nearly 25 pounds heavier on average. The average weight of men age 20–74 years increased from 166 pounds in 1960–62 to 191 pounds in 1999–2002 and the average weight of women increased from 140 pounds to 164 pounds during the same period.